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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/927,939	09/11/97	GRAINGER D	295.022US1

HM12/1112
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EXAMINER	
MERTZ,P	
ART UNIT	**PAPER NUMBER**
1646	14

DATE MAILED: 11/12/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/927,939	Grainger et al.
Examiner	**Group Art Unit**
Prema Mertz	1646

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- [x] Responsive to communication(s) filed on 10-12-99.
- [x] This action is **FINAL.**
- [ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

- [x] Claim(s) 1, 3-4, 6-11, 42-43 is/are pending in the application.
  - Of the above claim(s) _____ is/are withdrawn from consideration.
- [ ] Claim(s) _____ is/are allowed.
- [x] Claim(s) 1, 3-4, 6-11, 42-43 is/are rejected.
- [x] Claim(s) 42 is/are objected to.
- [ ] Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- [ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- [ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.
- [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.
- [ ] The specification is objected to by the Examiner.
- [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- [ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).
  - [ ] All [ ] Some* [ ] None of the CERTIFIED copies of the priority documents have been
  - [ ] received.
  - [ ] received in Application No. (Series Code/Serial Number) _____.
  - [ ] received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

- [x] Information Disclosure Statement(s), PTO-1449, Paper No(s). 11, 13
- [x] Notice of References Cited, PTO-892
- [ ] Notice of Draftsperson's Patent Drawing Review, PTO-948
- [ ] Interview Summary, PTO-413
- [ ] Notice of Informal Patent Application, PTO-152
- [ ] Other _____

Office Action Summary

*U.S. Government Printing Office: 1997 — 417-376/50309

DETAILED ACTION

1. Claims 2, 5 and 12-41 have been canceled in Paper No. 12, 10/12/99. Claim 10, amended claims 1, 3-4, 6-9, 11, and new claims 42-43 (Paper No. 12, 10/12/99), are under consideration.

Receipt of applicant's arguments and amendments filed in Paper No. 12 (10/12/99) is acknowledged.

2. The following previous rejections and objections are withdrawn in light of applicants amendments filed in Paper No. 12, 10/12/99:

(I) the objection to claims 3-12

(ii) the rejection of claims 1, 3-10 are rejected under 35 U.S.C. 101

(iii) the rejection of claims 1, 3-12 under 35 U.S.C. § 112, second paragraph

(iv) the rejection of claims 1, 3-4, 6-7 under 35 U.S.C. 102(b) as being anticipated by Rollins et al. (U.S. Patent No. 5,459,128), and

(v) the rejection of claims 1 and 8-10 under 35 U.S.C. 102(b) as being anticipated by Clark-Lewis et al. (1993) .

Applicant's arguments filed in Paper No. 12 (10/12/99), have been fully considered but were deemed persuasive in part. The issues remaining and new issues, are stated below.

Claim objections

3. Claims 9-10 and 42-43 are objected because of the following

There are sequences presented by both SEQ ID NO and the entire sequences themselves in claim 42. It is suggested that the amino acid sequences be identified only by the appropriate sequence

identifier as set forth in the "Sequence Listing" as required by 37 CFR § 1.821(d). Applicants are requested to remove the recitation of the sequences from the claims and simply recite the SEQ ID NO. Reciting both the SEQ ID NO and the sequences themselves is awkward, difficult to consider and increases the possibility of printer errors.

Furthermore, with respect to claim 43, there is a sequence recited which lacks description by the appropriate sequence identifiers (SEQ ID NO) set forth in the "Sequence Listing" as required by 37 CFR § 1.821(d). The sequences represented in claim 43, must have a separate sequence identifier for the sequence listing (SEQ ID NO).

Appropriate corrections for compliance are required.

Claim 9 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 10. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, first paragraph

4. Claims 1, 3-4, 6-11 and new claims 42-43, are rejected under 35 USC § 112, first paragraph.

This rejection is maintained for reasons of record set forth at pages 6-11 of the previous Office action (Paper No. 10, 4/7/99).

Applicants argue that the disclosure in the instant specification would enable the art worker to prepare chemokine peptides, variants or derivatives thereof, falling within the scope of the claims. However, contrary to Applicants arguments, the claims encompass both the C-C chemokines, as well

as the C-X-C chemokines, and known chemokines as well as those yet to be discovered. Furthermore, Applicants have themselves shown on the record, the unpredictability in the inhibitory activity of the broadly claimed chemokine variants (see page 104, Example 2), in which peptide 3 (7-12 of MCP-1) (SEQ ID NO:9), is a potent inhibitor of peptide 3 (1-12 of MCP-1) (SEQ ID NO:1). In contrast, peptide 3 (1-6 of MCP-1) (SEQ ID NO:8) was a much less potent inhibitor of peptide 3 (1-12 of MCP-1) (SEQ ID NO:1). Furthermore, peptide 3 (7-12 of MCP-1) (SEQ ID NO:9) showed no selectivity, inhibiting migration by all chemokines tested with an ED_{50} in the range of 7-9 μM. In addition, Applicants argue that derivatives of the peptide of the instant invention "may include" CRD, LRD and CFL derivatives of the peptide of the instant invention. In view of the fact that any arbitrary variant of the amino acid sequence of SEQ ID NO:1, would not be expected to confer the desirable inhibition of chemokine-induced cell migration activity, and in the absence of delimiting amino acid sequences that make up the functional domains of the instant peptides, a person of ordinary skill in the art would be unable to make variants and derivatives of the amino acid sequences embraced by the claims without undue experimentation to determine which amino acids retain the desirable biological activity.

Applicants citing In re Wands for the enablement is insufficient, and unpersuasive because in addition to the undue experimentation, there are substantial scientific reasons to doubt the scope of enablement, as set forth above. Applicants have compared this case with In re Wands, however, it is asserted that the instant situation differs significantly from that in Wands. As set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731,

737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), the factors to be considered under 35 U.S.C. § 112, first paragraph include (1) the breadth of the claims, (2) guidance presented, (3) the predictability of the art, and (4) quantity of experimentation. Wands involved antibody screening assays. Nine hybridomas had been isolated out of 143, and of those 4 fell within the scope of the claims, a 44% success rate. Compare this to the instant situation, where the amount of embodiments are innumerable, and the enabled embodiment amounts to those set forth in Tables 5-6. It is also asserted that if applicants were to randomly begin making fragments of not more than 30 amino acids, with at least 3 contiguous residues of the peptide corresponding to residues in the carboxyl-terminal half of the mature cytokine, the success rate, i.e. those which would have desirable inhibitory activity, would be much lower than 44%. There is little to no guidance as to which of these claimed peptides would possess the desirable activity.

The Courts in In re Wands 8USPQ2d, 1400 (CAFC 1988) determined that the repetition of work which was disclosed in a patent application as producing a composition containing an antibody, which is a naturally-occurring compound, did not constitute undue experimentation even if the antibody produced thereby was not identical to those that were disclosed in that application. In In re Wands the claims were drawn to a process and Applicants in Wands had described a repeatable process for production of the product. The instant claims are drawn to a product and Applicants have not described a repeatable process for obtaining the product as claimed.

Furthermore, the amount of embodiments corresponding to the desirable peptides, may be innumerable, and the enabled embodiments amount to only those set forth in Tables 5-6. Therefore,

there are substantial scientific reasons to doubt the scope of enablement, as set forth above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe any other peptides other than that whose amino acid sequence is shown in Tables 5-6, and since it is deemed to constitute undue experimentation to determine all the others, the disclosure is not commensurate with the scope of the claims. Therefore, Applicants are not enabled for a peptide having anything less than the amino acid sequence shown in Tables 5-6.

Applicants argue that the fact that single amino acid substitutions of alanine in hGH may result in changes in receptor binding affinity, does not provide evidence that the substitution of amino acids in a polypeptide results in a substituted polypeptide having a property that is wholly unpredictable. However, contrary to Applicants arguments, the issue here is not that substitution of amino acids in a polypeptide results in a substituted polypeptide having a property that is wholly unpredictable, but that substitution of amino acids by even conservative amino acid substitutions involves "undue experimentation" because predictability of which changes can be tolerated in a protein's amino acid sequence while retaining similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. To illustrate this issue, the Examiner has cited Cunningham et al. (1989) and George et al. (1988) references in the last Office Action. Applicants argue that in Cunningham et al the authors concluded that "small and local structural perturbations" were caused by the substitutions. This is because Cunningham intentionally chose and mutated only those residues

implicated in receptor binding. This is precisely the issue set forth by the Examiner, because in the instant case, Applicants have not disclosed which amino acids in the peptide are involved in binding to the receptor and that are likely to be critical for function. Furthermore, contrary to Applicants arguments, the regions that are important for chemokine peptide function have not been disclosed in the specification. There is no support in the instant specification regarding which regions of the protein are conserved and invariant, what amino acid substitutions would be tolerated, which regions of the protein can be mutated by deletions or insertions, by how many deletions or insertions or where in the protein and to what extent without affecting protein activity. The problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex. While it is known that many amino acid substitutions are generally possible in any given proteins sequence, the reasonable expectation of success is limited. Certain positions in the sequence are critical to a protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only relatively conservative or no substitutions (see Bowie et al., 1990, Science, Vol. 247, pg. 1306-1310, especially pg. 1306, column 2, paragraph 2). However, applicant has provided little or no guidance to enable one of ordinary skill in the art to determine without undue experimentation, the amino acids substitutions which render the protein tolerant to change and the nature and extent of change that can be made at these positions.

While enablement can be supported even if some experimentation is required, such experimentation must be merely routine and if the results to be obtained are unpredictable the experimentation is not routine, but rather undue. Applicants have not taught where the critical regions are in the instant peptides or related proteins nor what amino acid are conserved in the particular claimed proteins nor the structural requirements for producing compounds of similar activity. Thus, beyond the mere presentation of sequence data, applicants have provided little or no guidance which would, without undue experimentation, enable one of ordinary skill in the art to determine what positions, if any, in the protein are tolerant to change (e.g. such as by amino acid substitutions) and the nature and extent of changes that can be made and tolerated in the various positions. Without such guidance, the changes which can be made in the proteins structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is extensive and undue.

Applicants have cited case law, In re Marzocchi et al and Genentech Inc. v. NovoNordisk to support enablement by the instant specification. However, Applicants' arguments, citing In re Marzocchi for the proposition that the Examiner has failed to meet the burden and that the Examiner has not provided evidence inconsistent of Applicants disclosure is insufficient and unpersuasive, because there "are" substantial scientific reasons to doubt the scope of enablement as set forth above. Because of these reasons, one of skill in the art would not accept Applicants exemplary peptides to be representative of a C-C and C-X-C chemokines. The analysis set out by applicants is disagreed

with because this art is not predictable and there is no reason to think that results obtained with MCP-1 would be relied on by those in the art as guidance for all C-C and C-X-C chemokines.

In conclusion, the claims at issue are much broader in scope than even the claims in Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 18 U.S.P.Q. 2d, 1016 (see page 1026, section D), in which the claims to EPO were generic, covering "all possible sequences that will encode any polypeptide having an amino acid sequence 'sufficiently duplicative' of EPO to possess the property of increasing production of red blood cells." The instant claims are broader than the claims in Amgen because a structure and activity were recited in Amgen, however in the instant claims only an activity is recited, and an activity does not inherently follow from structure.

Claim Rejections - 35 USC § 112, second paragraph

5. Claim 11 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is vague and indefinite because it recites "cyclic reverse D sequence (CRD) derivative", rather than "cyclic reverse sequence derivative (CRD). It is unclear in the claim, as amended, if D denotes "derivative" or something else.

Conclusion

No claim is allowed.

Claim 42 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz Ph.D.
Primary Examiner
Art Unit 1646
October 25, 1999